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The Manitoba Human Papillomavirus vaccine surveillance and evaluation system

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Abstract

Background

With the recent introduction of a human papillomavirus (HPV) vaccine in Canada, it is important to establish surveillance and evaluation programs that not only track the uptake of the vaccine, but also assess its safety and its impact on: distribution of HPV type, cervical cancer screening programs, the incidence of anogenital warts, precancerous lesions and various cancers, and sexual behaviour.

Data sources and methods

Administrative databases, registries and questionnaire information are being linked to identify people receiving the HPV vaccine and to develop an evaluation system.

Interpretation

The availability of extensive linkable databases in Manitoba allows for the development of a comprehensive HPV vaccine surveillance and evaluation system that can address many of the questions related to the HPV vaccine. Aspects of the Manitoba surveillance and evaluation system could be implemented in other provinces that have similar databases.

Keywords

human papillomavirus vaccine, surveillance, evaluation, record linkage

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A quadrivalent human papillomavirus (HPV) vaccine was approved for sale in Canada in July 2006 for females aged 9 to 26 years. This vaccine protects against infection from HPV types 6, 11, 16 and 18. Types 16 and 18 are responsible for approximately 70% of all cervical cancers, while types 6 and 11 are responsible for over 90% of anogenital warts.[1-4] Clinical trials have shown that the vaccine is effective in preventing anogenital warts and precancerous cervical, vulvar and vaginal lesions.[5-9] A bivalent (types 16 and 18) HPV vaccine is currently going through the Canadian regulatory approval process, and other HPV vaccines that protect against an increased number of HPV genotypes are being evaluated.

Because most provinces and territories have implemented voluntary school-based vaccination, it is important to establish a surveillance and evaluation program that not only tracks uptake of the vaccine, but also assesses its safety and its impact on the distribution of HPV type, on cervical cancer screening, on the incidence of anogenital warts, precancerous lesions and various cancers, and on sexual behaviour.

The Canadian National Advisory Committee on Immunization statement on HPV vaccine noted an infrastructure gap in Canada, and that to evaluate the vaccine's effectiveness and impact, databases and registries must be developed and linked.[10] Others have also recognized the potential of linkable databases for evaluating vaccines.[11-15] Such databases allow for evaluation at a population level, as opposed to the restrictive setting of clinical trials. Through partnerships with Manitoba Health, CancerCare Manitoba and the Public Health Agency of Canada's

National Microbiology Laboratory, and with access to extensive linkable data resources, Manitoba is well-positioned to develop such a surveillance and evaluation system.

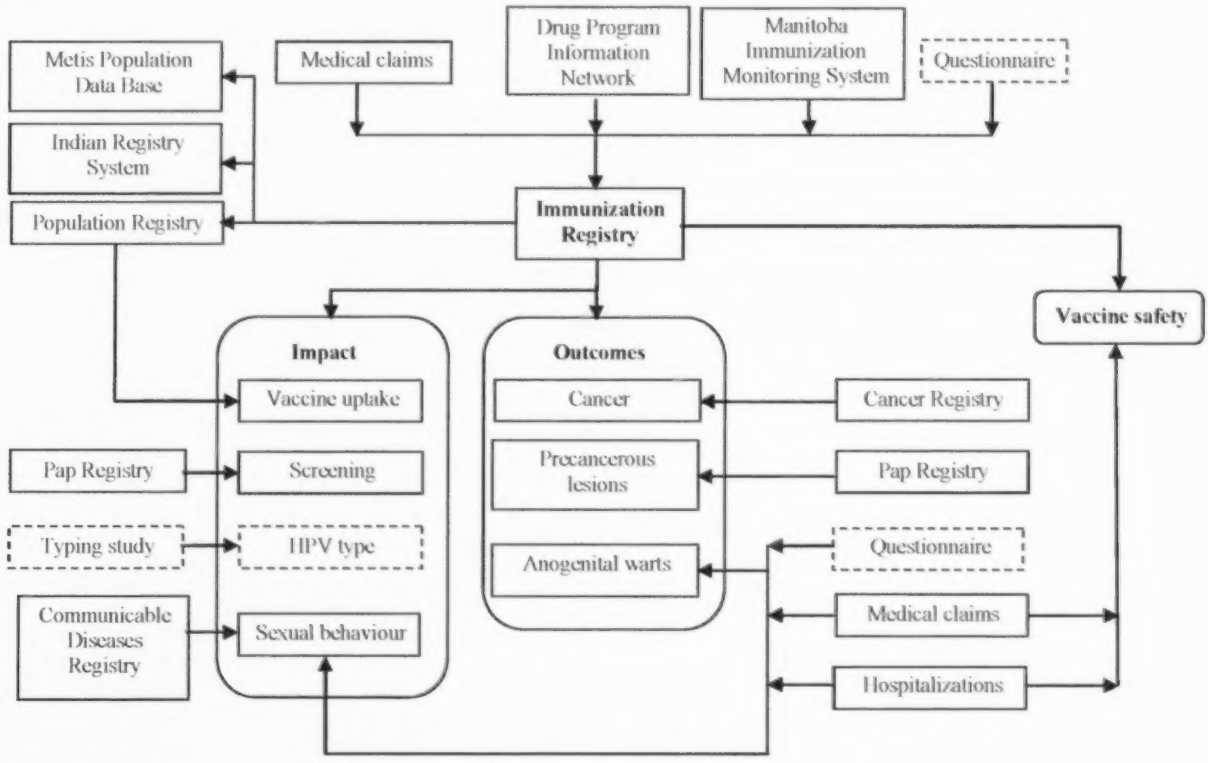
This paper describes specific aspects of the surveillance and evaluation system (Figure 1) that is being implemented in Manitoba (population 1.15 million).

HPV immunization registry

The backbone of any vaccine surveillance and evaluation program is an immunization registry. In Manitoba, such a registry is being developed from information in the Manitoba Immunization Monitoring System (MIMS - see www.gov.mb.ca/health/publichealth/cdc/surveillance/mims07.pdf), the Drug Program Information Network (DPIN), and medical claims. Females receiving the HPV vaccine through the school-based program are captured in MIMS. Those obtaining the vaccine outside the school-based program usually require a physician's prescription; the DPIN database includes most prescriptions filled in the province. This database allows for the identification of those who filled a prescription for the vaccine, but it is not possible to determine if they were actually vaccinated. However, given the cost of the vaccine (approximately $400 for three doses), it is unlikely that those who purchased it did not use it.

Anecdotal reports suggest that some Manitoba physicians provide the vaccine to their patients without a prescription. A potential source for identifying these patients is the medical claims database, which includes records of all claims submitted to Manitoba Health by physicians for payment for services. The tariff (billing) code 8891 has been specifically assigned to the HPV vaccine, although this code was not implemented until late 2008. Before that, physicians

Figure 1
Human papillomavirus (HPV) vaccine surveillance and evaluation system



could use 8800, which is a billable tariff code for any immunization. Physicians could indicate in the claim's comment field that the HPV vaccine was administered, but not all may have done so. Thus, the immunization registry will miss individuals whose physician gave them the vaccine without a prescription and submitted a claim with tariff code 8800, but did not specify HPV.

The immunization registry contains only non-identifying information such as the scrambled unique personal health identification number, date of birth, region of residence, date the prescription was filled, and date the vaccine was administered.

Aside from being essential for an effective evaluation of the vaccine, the registry will also be a means of contacting vaccinated individuals if safety issues arise or if booster doses are required. This is more effective than relying on the media or health professionals.[10]

Non-vaccinated females

The Manitoba surveillance system allows for the follow-up and comparison of outcomes in vaccinated and non-vaccinated females. All residents covered by the provincial health insurance are included in the Manitoba Population Registry (MPR), which is maintained by Manitoba Health to administer the insurance program. Since health insurance is provided free of charge, it covers more than 99% of the population. By linking the HPV immunization registry to the MPR, it is possible to identify females who have not been vaccinated. Loss of follow-up can be determined for both vaccinated and non-vaccinated females, as the MPR contains dates of termination of coverage through emigration or death.

Aboriginal peoples

Although HPV infection rates[16-18] and cervical cancer incidence and mortality rates[19-21] are higher in Aboriginal than non-Aboriginal females, little is know about the epidemiology of HPV among Aboriginal peoples. The uptake and impact of the vaccine may be different in Aboriginal populations.[22]

First Nations

As part of a Health Disparity Research Program at the Manitoba First Nations Centre for Aboriginal Health Research at the University of Manitoba, permission has been received from the federal Department of Indian and Northern Affairs to link the Indian Registry System (IRS) to the MPR. The IRS contains information on all registered First Nations as defined by the Indian Act, including reinstated First Nations under federal Bill C-31 legislation. With this link it is possible to undertake studies on vaccinated and non-vaccinated cohorts that include Registered First Nation status. However, approval must first be obtained from Manitoba's institutional review boards, which include First Nations ethical and health information decision-making bodies. To date, permission has been received to investigate HPV vaccine uptake, comparing Registered First Nations in Manitoba and all Manitobans, and permissions will be sought to examine broader aspects of the HPV vaccine surveillance program.

Métis

The Manitoba Metis Federation (MMF) Health and Wellness Department, in partnership with the Manitoba Centre for Health Policy and Manitoba Health, produced a province-wide Metis Health Status and Health Services Utilization study that created a large permanent updatable Metis Population Data Base (MPDB). The MPDB identifies the Manitoba Metis and exists under MMF ownership, control, access and stewardship. It is, in principle, possible to link the MPDB with the MPR to undertake a Metis-specific HPV vaccine surveillance and evaluation program. However, an agreement outlining the details of the program and authority from the MMF would be required, along with ethics and privacy approvals.

Vaccine uptake

With the development of the immunization registry, uptake of the vaccine in Manitoba is being tracked on a population basis. Specific questions that are being examined include:

- What are the overall and age-specific vaccination rates?
- How has uptake changed over time?
- What percentage of females receive fewer than the three recommended doses?
- Is uptake highest in areas of greatest need (for example, with the highest cervical cancer rates or lowest screening rates)?
- Does uptake vary by income quintile?

Among individuals with lower income, cervical cancer screening rates tend to be lower,[23-26] and cervical cancer incidence and mortality rates higher.[27,28] Cost is an important determinant of women's attitudes about receiving the vaccine, and household income has been associated with uptake.[29-31] Given the high cost, it would be expected that vaccination rates outside the school-based program would be lower among individuals with low income. Such inequity in access may well widen the difference between low- and high-income women in rates of anogenital warts and cervical abnormalities.

Vaccine impact

Cervical screening program

Some vaccinated females may develop a false sense of protection that could result in their no longer seeking screening.[32-34] Although the vaccine targets the oncogenic HPV types 16 and 18, it is essential that vaccinated females continue to be screened, as only about 70% of cervical cancers are caused by these two HPV types.[1-3] And some females may have been infected by these two types before vaccination or infected by other types of oncogenic HPV.

The Manitoba Cervical Cancer Screening Program was established in

January 2000, and the reporting of all cervical cancer screening tests to the program was mandated by law in 2001. A registry was established that contains demographic information for all women aged 18 to 69, and all Pap test, colposcopy and biopsy results. The registry also includes results for females outside the program's age range. By linking the immunization registry to the Pap registry, it will be possible to determine the impact of the vaccine on screening, in particular, whether screening rates of vaccinated and non-vaccinated women differ.

If females receiving the vaccine are those who would have been screened regularly, the vaccine will have less impact on reducing rates of cervical cancer.[35] Because a substantial number of Manitoba women aged 18 or older are being vaccinated, this possibility can be investigated by using the linked databases to examine the screening history of vaccinated and non-vaccinated women.

The vaccine will likely reduce the prevalence of cytological abnormalities, which, in turn, will lead to a decrease of the positive predictive value of Pap cytology.[33,36] Research is needed to evaluate the performance of cytology and HPV testing among vaccinated and non-vaccinated women, although because of ethical concerns, randomized trials may not be possible.[37] As described in the next section, a province-wide survey of HPV type was undertaken in Manitoba, the results of which will be included in the Pap registry. If such surveys continue, the accuracy of cytology versus HPV testing in vaccinated and non-vaccinated women can be determined by linking the immunization registry to the Pap registry. It would also be possible to determine if the HPV type is changing over time in women with lesions.

HPV type

A pilot study conducted in Winnipeg in 2007 and a larger province-wide study in 2008 collected HPV samples from approximately 900 women. HPV type is being determined by the Public Health Agency of Canada's National Microbiology Laboratory and the Cadham Provincial Laboratory of Manitoba Health. The results of the HPV tests are being entered into the Pap registry. Participants also completed a questionnaire on demographic, socio-economic, reproductive and lifestyle characteristics (http://www.cancercare.mb.ca/resource/File/Epi-Cancer_Registry/Questionnaire_For_Risk_Factors_Associated_With_Cervical_Cancer.pdf).

These studies will provide preliminary estimates of the prevalence of HPV types in Manitoba before widespread HPV vaccination. The intention is to repeat the survey periodically, although the frequency will depend on funding. These surveys will make it possible to determine whether the vaccine alters the infection rate and distribution of other HPV types, particularly other oncogenic types.[38] Based on the questionnaire information, differences in HPV type by the personal characteristics of survey participants will be examined.

Sexual behaviour

Concern has been expressed that HPV vaccination may lead to an increase in premature sexual activity and risky sexual behaviour.[33,39,40] The questionnaire for the Manitoba HPV typing study, which asks about sexual behaviour, could provide information on the sexual behaviour of vaccinated versus non-vaccinated females.

Although the impact of the vaccine on sexual behaviour cannot be directly assessed using the Manitoba databases, differences in pregnancy or birth rates between vaccinated and non-vaccinated women may be an indirect measure. Because virtually all births occur in hospital, linked immunization registry and hospital data can be used to determine birth rates in the two cohorts of women. And by including information from medical claims, pregnancy rates could also be estimated, although this would be less accurate than the data for births.

Differences between vaccinated and non-vaccinated women in the incidence of notifiable sexually transmitted infections may also provide indirect evidence of how the vaccine affected sexual behaviour. This information will be derived by linking the vaccine registry to the Manitoba communicable diseases registry.

If a sufficient number of older women are vaccinated, it will be possible to compare these indicators of sexual behaviour before and after vaccination.

Vaccine outcomes

Cancer

The Manitoba cancer registry was established in the 1930s and has been population-based since 1956. Because cancer is a notifiable disease and multiple sources of ascertainment are used, completeness in the recording of cases is considered to be very high.

In addition to causing most cervical cancer, HPV 16 and 18 are responsible for 80% to 90% of anal cancers. As well, varying proportions of vulvar, vaginal, urethral and head and neck cancers contain oncogenic HPV types.[33] Risk for these cancers can be determined by linking the Manitoba cancer registry to the cohorts of vaccinated and non-vaccinated females. However, given the rarity of these diseases, the cohorts must be followed for a substantial period before enough cases have occurred to test for differences. On the other hand, Manitoba may be able to contribute data to existing efficacy trials, such as the Nordic HPV vaccine trials, for a possible pooled analysis.[41]

Precancerous cervical lesions

While vaccination should, in the long-term, lead to a decrease in cervical cancer caused by HPV 16 and 18, in the short-term, a reduction in atypical squamous cells of undetermined significance and squamous intraepithelial lesions would be expected because of the shorter latency between HPV infection and development of these abnormalities.[36] Because the Pap registry includes cytological results for all Pap tests undertaken in Manitoba and colposcopy and histological information, abnormality rates among the vaccinated and non-vaccinated can be calculated.

What is already known on this subject?

- A quadrivalent HPV vaccine was approved for sale in Canada in July 2006.
- Most provinces and territories have implemented school-based vaccination programs.
- Questions remain about the vaccine's safety and its impact on anogenital warts, cervical abnormalities, cervical cancer screening, HPV type, and sexual behaviour.

What does this study add?

- This article explains how linkable databases and registries available in Manitoba and other Canadian provinces and territories can be used to address questions about the HPV vaccine.

Anogenital warts

Given the short time between exposure to HPV and the development of anogenital warts, they are one of the first indicators of the success of a vaccination program.[42] For the 1985 to 2004 period, medical claims and hospitalization records were linked to identify men and women with anogenital warts for a study of incidence and prevalence trends in Manitoba.[43] The methodology developed in that study will be employed to create an on-going registry of cases of anogenital warts. This registry will be employed to document the impact of the vaccine on the incidence and prevalence of anogenital warts, and by linking it to the immunization registry, to determine the effectiveness of the vaccine in preventing anogenital warts. Although the vaccine has not been recommended for males, an anogenital warts registry will make it possible to determine if vaccinating females reduces the incidence of anogenital warts in males.

Vaccine safety

After reviewing data on events occurring up to six years after vaccination, the World Health Organization concluded that the evidence for the safety of the HPV vaccines was "reassuring."[44,45] However, "long-term safety data are essential for an HPV vaccine, since it will likely target hundreds of millions of young, healthy individuals worldwide who are otherwise not subject to epidemiological surveillance..."[38] Furthermore, the safety results to date are based on carefully controlled clinical trials, the participants in which are subjected to strict eligibility criteria. Studies that examine the safety of the vaccine in real world population-based settings are required.

Because many vaccinated females will be in, or about to enter, their reproductive years, it is important to determine if the vaccine results in reproductive toxicities or increases the risk of adverse pregnancy outcomes.[33,38] It has been suggested that the vaccine may have a positive impact on pregnancy outcomes by reducing the number of women treated for precancerous cervical lesions.[33] Procedures used to treat these lesions, such as loop electrosurgical excision and cold knife conization, have been associated with preterm delivery, low birth weight, caesarean section, and premature rupture of membranes.[46]

Canada, like many other countries, has a surveillance system that tracks adverse events following vaccination.[12] A recent report[47] based on the American system found that, except for syncope and venous thromboembolic events, the rates of adverse events after receiving the HPV vaccine were no greater than those for other vaccines. However, these results tend to be based on voluntary notification and underestimate the actual number of events. And because no information is available for a comparative non-vaccinated cohort, determining causality is difficult. By linking medical and hospitalizations records to the immunization registry, as has been called for by Brotherton et al.,[48] it will be possible to undertake a long-term follow-up on a population basis to determine if the vaccinated group is at increased risk for any medical conditions. A similar method is being used in the Nordic trials.[41]

Mathematical modeling

Mathematical models, such as those developed by Brisson and colleagues,[49,50] are currently part of the overall evidence base used to inform decision-making about HPV vaccination and cervical cancer screening programs in Canada.[22] Models can also be an intrinsic part of an ongoing HPV vaccine surveillance program, particularly the long-term impact of the vaccine. An individual-based dynamic model of HPV transmission, infection and disease, including screening and vaccination, can be developed with data from the various Manitoba databases and registries. Integration of models and surveillance will allow:

- better understanding of emerging epidemiologic trends after vaccination (for example, changes in age at infection, waning effectiveness, herd-immunity, HPV type replacement).
- improved predictions of the effectiveness and cost-effectiveness of HPV vaccination and cervical cancer screening (for example, projections based on up-to-date data).
- adjustment and optimization of HPV vaccination and cervical cancer screening strategies (for example, reduce number of doses, change vaccine schedule, revisit screening paradigms).

Conclusion

Surveillance of vaccine coverage and safety is critical for a successful immunization program.[51] Erickson et al. have outlined the requirements for an evaluation of an immunization program, which include the availability of information systems to measure coverage, reduction of disease incidence, complications, sequelae and mortality,

and adverse events associated with vaccination, and to link health outcomes databases, immunization registries and population registries.[14] The essential role of linked databases in evaluating the HPV vaccine's effectiveness has also been noted by others in Canada and elsewhere.[10-13,22,52,53] The participants in the Canadian HPV Vaccine Research Priorities Workshop rated the importance of such linkages as high, but they considered feasibility to be low.

Manitoba has a long history of record linkage, facilitated by the inclusion of a unique Personal Health Identification Number in most databases. The Manitoba databases are as comprehensive as those being used in the Phase III and IV Nordic trials. Information arising from the surveillance and evaluation system will provide data on many questions related to the vaccines' uptake, impact and safety. Aspects of the Manitoba surveillance and evaluation system could be implemented in other provinces that have similar databases. Also, policy makers and/or researchers who have questions about the HPV vaccine that are not being addressed by the current surveillance system and evaluation program could, with the appropriate local ethics and privacy approvals, obtain access to the necessary information from the registries and databases that form the basis of the Manitoba surveillance system. ■

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